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NEURAL REGULATION OF THE BIOCHEMICAL PROCESSES
OF NERVE ACTIVITY (ACTIVITY OF CHOLINESTERASE)

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Clinical study of human endocrine diseases and laboratory observations of animals, the functions of whose endocrine glands have been experimentally disrupted, always afford clearly defined evidence of a disturbance in the nervous system. These nervous disturbances are frequently the primary factor compelling a patient to consult a physician. Functional disorders of the nervous system affect all the branches of the system, and may be made manifest in various ways: insomnia, a general state of excitement, somnolence, apathy, inability to concentrate, various disturbances of the digestive tract, skin diseases, and regulatory disturbances in the cardiovascular system and other physiological systems of the organism. These phenomena, which are connected with functional disorders of the nervous system, are peculiar, in many of their manifestations, to numerous endocrine disorders. This attracted our attention, and prompted our laboratory many years ago to undertake the study of the problem involved in the neural regulation of physiological functions in cases of endocrine imbalance.

Endocrine disturbances cause marked changes in the internal environment of an organism. The unusual complexity of this problem caused us to include in our study of the physiological mechanisms an investigation of intimate biochemical processes connected with the functions of the nervous system. This article deals with some of the data obtained in our research.

All the functions of an organism, the entire "internal world" of animals and men, is under the constant regulatory influence of the higher divisions of the central nervous system, i.e., the cerebral cortex. I. P. Pavlov formulated this postulate in the following way, "This higher divisions control all the phenomena occurring in the body. ... The more perfect the central nervous system of an animal organism is, the more centralized it is, and the more does its higher division determine and define the entire activity of the organism" (Ref 1, 1935, pp 409-410).

Impulses arising in the internal organs of an organism are exceptionally important to the functional condition and constant tonus of the cerebral cortex. "These irritations arising in the internal organs, even though we may not be aware of them, nevertheless constantly maintain the high tonus of the cerebrum" (Ref 1, 1935 p 421).

Concomitant with the study of the interrelationships between an organism and its external environment, the problem of the processes occurring within the organism itself was ever present in the mind of I. P. Pavlov. He wrote: "In the cortex, together with a grandiose representation of the outside world through the afferent fibers (and this is an essential condition of the higher regulatory functions), there is also a wide representation of the internal world of an organism, i.e. the operational condition of the mass of organs and tissues, and the mass of internal organic processes" (Ref 1, 1932, p 140).

- 1 -

STAT

The problem of the effect of an irritation which arises in an internal organ and affects the activity of the cerebrum has been thoroughly elaborated by K. M. Bykov and his associates (2). Their efforts also show the important role of the humoral factor and of the hormonal activities of the endocrine glands in the cortical process which regulates the functions of the internal organs. The works of Balakshina (3), Bykov and Alekseyev-Berkman (2), Kel'man (4), Ol'yanskaya (5), and others also demonstrate the participation of the endocrine glands (the hypophsic, the suprarenal, and the thyroid) in the process by which the cerebral cortex regulates the activity of the internal organs and of the various tissue processes.

A cessation or disturbance of the functions of the endocrine glands disrupts the operation of all branches of the cerebral nervous system, and primarily that of its higher divisions. Associates of I. P. Pavlov made numerous observations in this field. For a review of this work see A. G. Ivanov-Smolenskiy (6).

Insofar as all nerve processes are based essentially on a physicochemical mechanism, disturbances in the nerve process observed in cases of endocrine imbalance are likewise based on changes in the physicochemical reactions occurring in the organisms. This assumption was frequently emphasized by I. P. Pavlov in a number of his works. In one of them, he wrote, "It is self-evident that besides such particular questions regarding disturbances of normal nerve activity, another problem still faces physiologists, the problem of the physicochemical mechanism of the most elementary processes: irritation and inhibition and their interrelationships and overstrains" (1).

The physicochemical processes taking place in nerve tissues include the humoral link, which is active during the transmission of a nerve impulse. The concept of the humoral link, as we understand it, includes mediators (acethylcholine, sympathin) released by the activity of the nervous system, products of metabolism occurring in the nerve tissues and in the innervated organs and tissues, and hormones from the endocrine glands. The importance of the vitamins which participate in the complicated biochemical reactions involved in nerve stimulation must not be forgotten. Thus, for example, Vitamin B_1 is an indispensable component of carbohydrate metabolism, i.e., of a series of processes which play an important part in the activity of the nervous system at all of its levels.

In our research we proceeded from the assumption that whenever disturbances of endocrine activity take place, which always produce changes in the functional condition of all divisions of the nervous system, including that of the cerebral cortex, changes in physicochemical processes occur. One of the components of the complicated and numerous biochemical processes is acethylcholine metabolism, which actively participates in the operation of the nervous process.

The works of our laboratory which have already been published (6, 7, 10) indicate that in various pathological conditions, including endocrine disturbances, the liberation of mediators (sympathin or acetylcholine-like substances) occurs in amounts qualitatively and quantitatively capable of producing a reaction corresponding to that induced by the given mediator in a normal organ of a normal organism. These phenomena occur at the level of the terminal ends of the vegetative nerve fibers, notwithstanding inversion of the effect or absence of an effect on the organ upon irritation of these fibers. In an organism in which pathological conditions exist, i.e., intoxocation or functional disorders of the endocrine glands due, for example, to the removal of the hypophysis or the suprarenal glands, the irritation of the nerve conductors may produce either no reaction on the part of the organ, or an inverse effect.

- 2 -

STAT

The data in this article concern the problem of clarifying the changes in the activity of the enzyme which decomposes acetycholine in an organism, i.e., cholinesterase. We consider it essential to clarify the nerve mechanism which regulates the activity of cholinesterase, which, together with the other enzymes and biochemical components of nerve activity, participates in the intimate re-actions that bring about the nervous processes. In one series of experiments we studied the effect of the irritation of nerve fibers on the activity of cho-linesterase present in the tissues of organs. In another series we traced the effect of the severing of a nerve and of its consequent degeneration on the activity of the cholinesterase present in tissues of the same organs. In a third series of experiments we determined the role of endocrine factors in the neural regulation of cholinesterase activity.

The research was conducted at various times of the year using frogs. A detailed account of the experiments is given in the works of Baranove (8). In order to determine the effect of irritation of the nervous system on the activ-ity of cholinesterase, we irritated the vegetative nerve fibers which innervate various organs. We observed the effects of irritation of the sympathetic and parasympathetic nerve fibers that innervate the liver, and of the sympathetic fibers of skeletal muscles which were in a tonic or tetanic state. For these experiments, we used the forearm and sural muscles of a frog. Research was also done on the activity of cholinesterase in cases where there was complete denervation of these muscles.

Experimental irritation of the sympathetic nerve fibers of the liver either increased or decreased the activity of cholinesterase. Similar changes were also observed when the parasympathetic nerve fibers were irritated. These changes, however, were less pronounced, and showed a tendency toward a decrease in activity (Fig 1).

Irritation of the parasympathetic nerve fibers which innervate the skeletal muscles also caused some changes in the activity of the enzyme. These changes however, were considerably less intensive than those observed when the sympa-thetic fibers which innervate the liver were irritated. The activity of cho-linesterase in groups of skeletal muscles with differing functions showed var-ious changes. In the muscles of a frog's forearm, which may also function as tonic muscles in connection with the seasonal change in metabolism during spring time, the activity of cholinesterase changed considerably when the nerve fibers were irritated. However, in the sural muscles, whose function remains the same during all seasons, the activity of the enzyme showed little varia-tion (Fig 2).

It should be noted that the cholinesterase activity in these functionally different groups of skeletal muscles varies even without irritation of the sympathetic nerve fibers which innervate them. In a series of experiments in which we compared the activity of cholinesterase in the muscles of the forearm (functioning in the spring as a tonic-type muscle), and the hip (tetanic), and in the straight muscles of the abdomen (tonic) and sural muscles (tetanic), our observations revealed that this activity was appreciably higher in tonic muscles than in tetanic muscles. Changes in the activity of cholinesterase in tetanic muscles were observed more rarely. Such changes were relatively in-significant in magnitude.

In order to determine the role of the motor nerves in the regulation of the activity of cholinesterase, we observed the activity of this enzyme in the totally denervated forearm and sural muscles of an animal (frog) and compared it with the activity in the same muscles of normal extremities of the same animal. The majority of experiments showed a slight decrease in the activity of cholinesterase in a denervated extremity as compared with this activity in the normal extremity used as a control. These changes were expressed some-what more definitely in the muscles of the forearm than in the sural muscles.

- 3 -

STAT

The activity of cholinesterase in the liver and the skeletal musculature changes under the influence of impulses transmitted by the vegetative nerve fibers. These impulses may cause rapid shifts in the activity of the enzyme.

In contrast to the rapid emergency readjustments produced in an organism by nerve impulses, the hormones secreted by the endocrine glands as a result of the action of the nervous system, especially the cerebal cortex, also produce functional readjustments of the organs and tissues. These readjustments, however, occur much more slowly. We observed the regular character of such changes in relation to cholinesterase activity. These changes definitely occur during endocrine disturbances, and not only in pathological conditions of an organism; they can be easily detected in normal frogs during the seasonal readjustment of metabolism, especially during the spring.

Our experiments show that the activity of cholinesterase in the liver of normal frogs during the spring is considerably lower than that in the muscles of the forearm, while in the fall, it is higher. This may be explained by the frog's winter periods of starvation, which cause a sharp decrease in the glycogen content of its liver.

The importance of carbohydrate metabolism for the acetylcholine metabolism has been established by a series of experiments. Changes in activity which depend on different concentrations of glucose have been observed during experiments in our laboratory both in vitro and in vivo.

Our next task was to trace the changes occurring in the activity of cholinesterase in the liver and skeletal musculature after the removal of certain endocrine glands. In 1947 in our laboratory, I. M. Dzhakson (9) determined that the ability of the liver to destroy acetylcholine was decreased by the removal of the hypophysis. Further research demonstrated that this ability was due to the presence of cholinesterase in the liver, and that the activity of this enzyme changed in accordance with the functional state of the entire organism, particularly the liver.

Since the suprarenal glands, especially their cortex, influence all types of metabolism, including carbohydrate and salt metabolism, we assumed that the removal of the suprarenal glands would be reflected in the activity of cholinesterase in the liver and the skeletal muscles of an animal. We based this assumption on the data elaborated above, which demonstrate the connection between the functional state of an organ and its acetylcholine metabolism. In fact, after we had removed the suprarenal glands of a frog, we observed a considerable change in the activity of cholinesterase in the liver and skeletal musculature. The activity of cholinesterase in the liver in the majority of experiments showed a considerable decrease, as compared to the liver of normal frogs, and the activity of cholinesterase in various groups of skeletal muscles decreased more in tonic muscles than in tetanic muscles. The skeletal muscles which are subject to more marked functional changes during the seasonal readjustments of their metabolism, i.e., the muscles of the frog's forearm, also undergo essential changes (frequently a decrease) in the activity of cholinesterase after the removal of the suprarenal glands.

We also observed the above relationships in experiments on warm-blooded animals, i.e., rats whose suprarenal glands had been removed.

Irritation of the sympathetic and parasympathetic nerve fibers which innervate the liver, and of the sympathetic fibers leading to the skeletal muscles, does not produce any change in the activity of cholinesterase in animals whose suprarenal glands have been removed. The slight changes in this activity in the skeletal muscles of such animals after the total denervation of these muscles are even less pronounced.

- 4 -

STAT

Consequently, where a change in the acetylcholine metabolism has occurred, as noted in animals whose adrenal cortex is deficient, nerve impulses transmitted by the central nervous system through vegetative and motor nerve fibers cannot elicit the reaction which usually occurs in normal animals, i.e., they do not produce changes in the activity of cholinesterase.

The observations which we have made concern only one small link in the long chain of chemical processes which occur in the course of activity concomitant to the transmission of a nerve impulse, i.e., they pertain only to activity of the enzyme which decomposes acetylcholine in the organism. We are continuing our work in this field, and in the near future intend to present experimental data which will bring us closer to an understanding of the manner in which endocrine disorders and other pathological conditions modify the intimate processes of the nervous system.

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STAT

Irrigation
of the
Vagus Nerve

Irrigation
of the
Sympathetic
Nerve Fibers

Forearm
Muscle

Sural
Muscle

56% 44%   32% 40% 28%   39% 36% 25%   15% 26% 59%

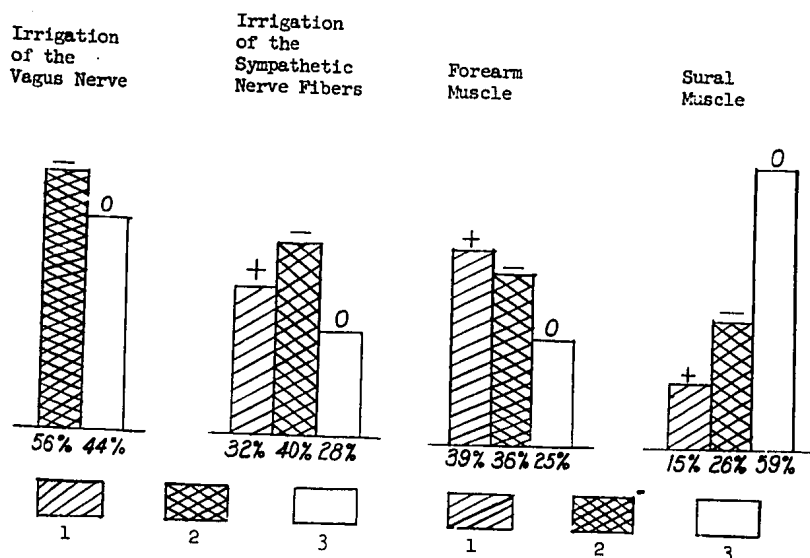1   2   3   1   2   3

Figure 1. Changes in the activity
of cholinesterase caused
by the irritation of the
vegetative nerve fibers
which innervate the liver
(in percentages of ex-
periments):
1. Increased activity
2. Decreased activity
3. No change in activity

Figure 2. Changes in the activity
of cholinesterase in
skeletal muscles caused
by the irritation of the
sympathetic nerve fibers
which innervate them (in
percentages of experi-
ments):
1. Increased activity
2. Decreased activity
3. No change in activity

STAT

- 6 -